PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 September 1999 (01.09.99)	
International application No. PCT/AU99/00062	**Applicant's or agent's file reference** FP10641
International filing date (day/month/year) 29 January 1999 (29.01.99)	**Priority date** (day/month/year) 29 January 1998 (29.01.98)
Applicant JACKSON, Roy, William et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

19 August 1999 (19.08.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. Carrié
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

European Patent Office

SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 99 90 3533

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	FR 2 296 420 A (LABORATORIOS DEL DR. ESTEVE, S.A.) 30 July 1976 (1976-07-30) * complete document *	1,2,4,5, 23	C07D489/02 C07D489/04 C07D489/12 C07D221/28 C07D223/06 C07D211/32 C07D211/64 C07D223/14 C07D221/26 A61K47/48
X	WO 95 18186 A (ARRIS PHARMACEUTICAL CORPORATION) 6 July 1995 (1995-07-06) * example 33 *	1	
X	US 5 610 283 A (KENNETH F. BUECHLER) 11 March 1997 (1997-03-11) * examples 9,10,13-16 *	1	
X	EP 0 004 960 A (ACF CHEMIEFARMA NV) 31 October 1979 (1979-10-31) * claims *	1	
X	US 3 928 359 A (GERHARD WALTHER ET AL.) 23 December 1975 (1975-12-23) * claims *	1	
X	US 3 341 538 A (FRED B. BLOCK ET AL.) 12 September 1967 (1967-09-12) * examples 13-15 *	1	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D
A61K

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

Place of search	Date of completion of the search	Examiner
THE HAGUE	10 July 2003	Van Bijlen, H

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C04)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 90 3533

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

10-07-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2296420 A	30-07-1976	FR 2296420 A1	30-07-1976
WO 9518186 A	06-07-1995	WO 9518186 A1	06-07-1995
		AU 689764 B2	09-04-1998
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US 5610283 A	11-03-1997	AT 180484 T	15-06-1999
		AU 3941893 A	08-11-1993
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		DE 69325096 D1	01-07-1999
		DE 69325096 T2	30-09-1999
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		AT 373585 B	10-02-1984
		AT 307579 A	15-06-1983
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		IL 57129 A	30-12-1983
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US 3928359 A	23-12-1975	DE 2245141 A1	21-03-1974
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 90 3533

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The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

10-07-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3928359 A		AT 932574 A	15-03-1976
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		AU 6030173 A	13-03-1975
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		BG 21229 A3	20-03-1976
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		CS 168678 B2	29-06-1976
		CS 168679 B2	29-06-1976
		CS 168680 B2	29-06-1976
		DD 109384 A5	05-11-1974
		ES 418563 A1	01-05-1976
		ES 430197 A1	16-10-1976
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		ES 430202 A1	16-10-1976
		ES 430203 A1	16-10-1976

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 90 3533

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3341538 A	12-09-1967	NONE	

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 489/02, 489/04, 489/12, 221/28, 223/06, 211/32, 211/64, 223/14, 221/26, A61K 47/48

A1

(11) International Publication Number: WO 99/38869

(43) International Publication Date: 5 August 1999 (05.08.99)

(21) International Application Number: PCT/AU99/00062

(22) International Filing Date: 29 January 1999 (29.01.99)

(30) Priority Data:

PP 1530	29 January 1998 (29.01.98)	AU
PP 3114	21 April 1998 (21.04.98)	AU
PP 5046	4 August 1998 (04.08.98)	AU

(71) Applicants *(for all designated States except US)*: MONASH UNIVERSITY [AU/AU]; Wellington Road, Clayton, VIC 3168 (AU). POLYCHIP PHARMACEUTICALS PTY. LTD. [AU/AU]; Technology House, 6–8 Wallace Avenue, Toorak, VIC 3142 (AU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: JACKSON, Roy, William [AU/AU]; 30 Through Road, Burwood, VIC 3125 (AU). SUBASINGHE, Kamani, Rupika [AU/AU]; 11 Ilora Court, Glen Waverley, VIC 3150 (AU). BOURA, Alan, Louis, Arthur [AU/AU]; Monash University, Dept. of Pharmacology, Wellington Road, Clayton, VIC 3168 (AU).

(74) Agent: SANTER, Vivien; Griffith Hack, 3rd floor, 509 St. Kilda Road, Melbourne, VIC 3004 (AU).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: THERAPEUTIC COMPOUNDS

(57) Abstract

This invention relates to novel structural analogues and derivatives of compounds with general analgesic or related pharmacological activity. In particular the invention relates to derivatives of opioid compounds, particularly morphine and related compounds, in which an opioid compound is linked via the nitrogen at position 17 to a spacer group, which in turn is linked to a charged group, or a pharmaceutically acceptable salt thereof. In particularly preferred embodiments the opioid compound is morphine, codeine or buprenorphine.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
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EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00062

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: C07D 489/02, 489/04, 489/12, 221/28, 223/06, 211/32, 211/64, 223/14, 221/26; A61K 47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
-

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN: FILE CA Substructure Search and CAS-ONLINE Keyword search:
(Ketobemidone OR Ethoheptazin OR Eptazocin OR Pentazocin) and (amidin OR guanidin)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts 117:82892, Clin. Exp. Pharmacol. Physiol. (1992), 19 (11) pages 17-23 RN 142740-96-3 RN 142740-97-4	1 to 7, 14, 16, 17, 22 to 26
A	US 4806556 (Portoghese, Philip S, et al) 21 February 1989 See whole document especially abstract	1 to 7, 14, 16, 17, 22 to 26

☐ Further documents are listed in the continuation of Box C

☒ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 March 1999	- 9 MAR 1999
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer **CHRISTINE BREMERS** Telephone No.: (02) 6283 2313

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 99/00062

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member	
US	4806556	US	4730048
			END OF ANNEX

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

04 AUG 2000

PCT

Applicant's or agent's file reference VS:WS:FP10641	**FOR FURTHER ACTION** See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).	
International application No. **PCT/AU 99/00062**	International filing date *(day/month/year)* 29 January 1999	Priority Date *(day/month/year)* 29 January 1998

1625

International Patent Classification (IPC) or national classification and IPC

Int. Cl.[6] C07D 489/02, 489/04, 489/12, 221/28, 223/06, 211/32, 211/64, 223/14, 221/26, A61K 47/48

Applicant

MONASH UNIVERSITY

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

[X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 7 sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

Date of submission of the demand 19 August 1999	Date of completion of the report 19 January 2000
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **IAN DOWD** IJDowd. Telephone No. (02) 6283 2273

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU 99/00062

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1-9, 11-34,** as originally filed,
pages , filed with the demand,
pages **10,** filed with the letter of **21 December 1999**.

☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **35-40**, filed with the letter of **21 December 1999**.

☒ the drawings, pages **1-3,** as originally filed,
pages , filed with the demand,
pages , filed with the letter of .

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , filed with the letter of .

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, ~~unless otherwise~~ indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-40	YES
	Claims		NO
Inventive step (IS)	Claims	1-40	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-40	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Document (1): Chemical Abstract Vol. 17, abstract no. 82892
Document (2): US A 4806556 (Portoghese) 21 February 1989

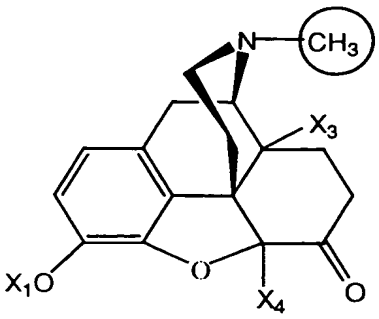
D1 discloses compounds of the general formula (1), [opioid-N]-[spacer]-[charged group], as per claim 1, with an unsubstituted straight chain three carbon alkyl spacer as per claims 2, 4 and 5, and a guanidine charged group as per claim 6. General formula (II) of claim 7 where the opioid is of formula YN-R, is also disclosed. However, D1 does not disclose that any of the compounds possess activity at opiate receptors, and hence activity as a peripherally acting analgesic. This "negative" disclosure would steer the person skilled in the art away from further investigation with this class of compounds. Therefore, the claims are novel and possess and inventive step with regard to citation D1.

D2 discloses compounds of the general formula (1) of claim 1, with the difference of the nitrogen at position 17 is substituted by alkyl, cycloalkyl, aryl, aralkyl or alkenyl (exemplified by propyl), whereas in the present application the nitrogen at position 17 is substituted with a charged group (exemplified by amidine or guanidine). Therefore the claims can be considered to be novel. An inventive step is also acknowledged as there is no disclosure or suggestion that substitution of charged groups at position 17 would be envisioned or an advantage.

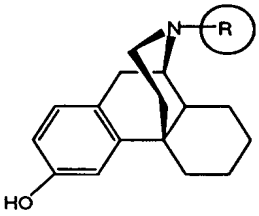
VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

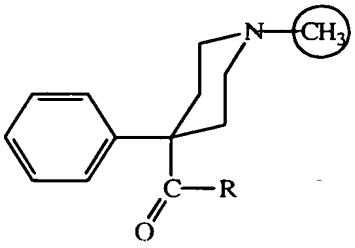
Claim 25 relates to a method of treating a human. Some signatory states do not allow methods of treatment of the human body. As Australia does not object to such methods it has been included in this report.



X_1	X_3	X_4	Name
CH_3	H	H	Hydrocodone
H	H	H	Hydromorphone
H	OH	H	Oxymorphone
CH_3	OH	H	Oxycodone
H	H	CH_3	Metopon

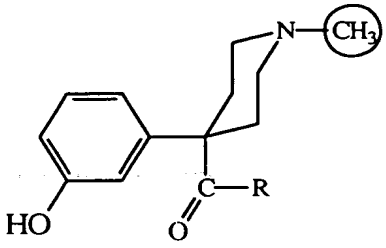


R	Name
$PhCH_2CH_2$	Phenomorphan
CH_3	Levorphanol



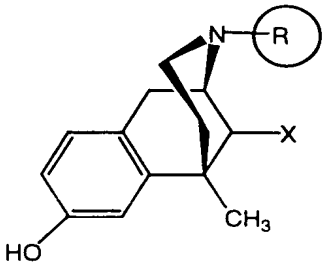
$R = CH_3CH_2O$

Ethoheptazine

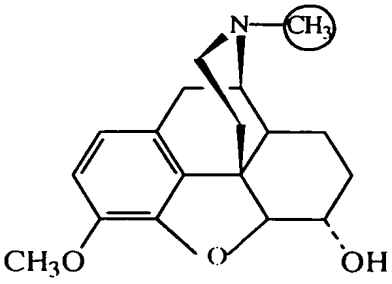


$R = CH_3CH_2-$

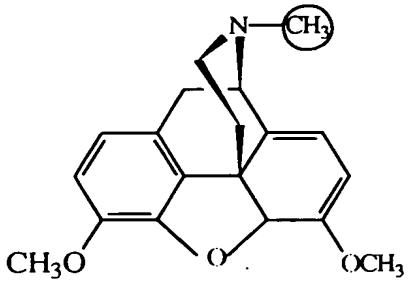
Ketobemidone



R	X	Name
CH_3	H	Eptazocine
$Me_2C=CHCH_2-$	CH_3	Pentazocine



Dihydrocodeine



Thebaine

The claims defining the invention are as follows:

1. An opioid compound of general formula I

[opioid-N]-[spacer]-[charged group],

I

where said opioid compound has activity at opiate receptors,

in which an opioid compound is linked via the nitrogen at position 17 to a spacer group, which in turn is linked to a charged group,

or a pharmaceutically acceptable salt thereof,

where said opoid compound has activity at opiate receptors.

2. A compound according to Claim 1, in which the spacer is a straight or branched alkyl, alkenyl or alkenyl chain of 1 to 6 carbon atoms, which may optionally be substituted.

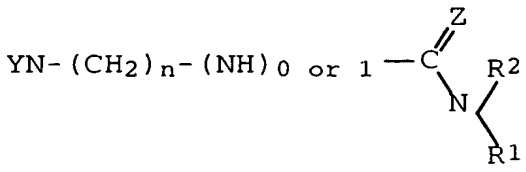
3. A compound according to Claim 1, in which the spacer is a cyclic alkyl, alkenyl or alkynyl group, which may optionally be substituted.

4. A compound according to any one of Claims 1 to 3, in which the spacer group is unsubstituted.

5. A compound according to any one of Claims 1 to 4, in which the spacer group is of 2 to 3 carbon atoms.

6. A compound according to any one of Claims 1 to 5, in which the charged group is an amidine or guanidine group.

7. A compound according to Claim 1, of general formula (II)



in which

YN- represents an organic residue obtained by removal of the R group from an opioid compound of general formula

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

or of the general formula

$$Y^1\text{-}N(R^4)\text{-}R$$

(IIIb)

wherein R^4 is methyl or ethyl, and

Y^1-NR^4 represents the corresponding organic residue;

Z is O, S or NR^3;

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

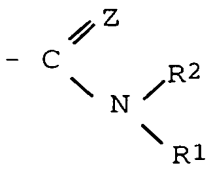
R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

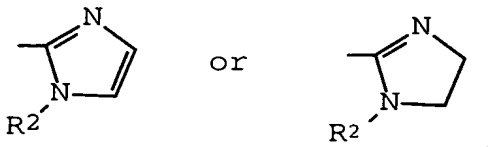
R^1 and R^3 may together complete an addition ring, or a pharmaceutically acceptable salt thereof.

8. A compound according to Claim 7, in which R^1 and R^3 together complete an addition ring, and the grouping



forms a heterocyclic moiety.

9. A compound according to Claim 8, in which the heterocyclic moiety is a 2-imidazolyl or 2-imidazolinyl group of formula:



10. A compound according to Claim 8 or Claim 9, in which R is CH_3.

11. A compound according to any one of Claims 8 to 10, in which n is 2 or 3.

12. A compound according to any one of Claims 8 to 11, in which Z is NH, and R^1 and R^2 are both H.

13. A compound according to any one of Claims 8 to 11, in which the precursor of YN- or Y^1NR^4- is a compound selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, etorphine, acetorphine, ketobemidone, ethoheptazine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine and metazocine.

14. A compound according to Claim 12, in which the precursor of YN- or Y^1NR^4- is morphine, codeine or buprenorphine.

15. A compound according to Claim 1, in which the opioid compound of formula (IIIa) is selected from the group set out in Table 1.

16. A compound according to Claim 1, in which the opioid compound of formula I is selected from the group consisting of KRS-41, KRS-2-19, KRS-3-7, KRS-3-23-4, KRS-3-28, KRS-3-30-2, KRS-3-56, KRS-2-63, KRS-4-8, and KRS-2-47, as herein defined.

17. An opiate receptor agonist having analgesic properties and having reduced or no CNS activity, of general formula I or general formula II as defined in any one of claims 1 to 15.

18. A method of reducing the central nervous system activity of an opioid compound, comprising the step of linking the nitrogen atom at position 17 of said compound to a spacer group, which in turn is linked to a charged group.

19. A method for the preparation of a compound of formula II as defined in any one of Claims 8 to 13, in which YN- may be replaced by Y^1NR^4-, comprising the steps of

(a) Reaction of a compound of formula

YN-H

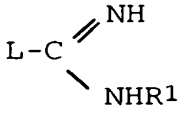
(IV)

with a cyanamide, R^1NHCN, according to the equation

$$YN\text{-}H + R^1NHCN \rightarrow YN\text{-}C(=NH)\text{-}NHR^1$$

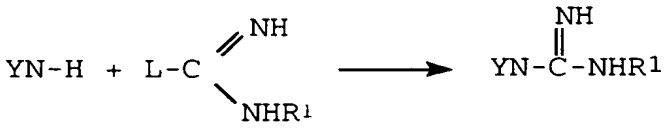
or

(b) Reaction of a compound of formula (IV) with a compound of formula



(V)

wherein L is a leaving group, according to the equation



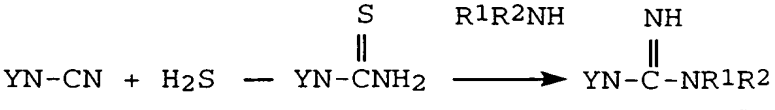
20. A method for the preparation of a compound of formula II as defined in any one of Claims 8 to 13 in which Z is NR^2, comprising the steps of

(a) Reaction of a compound of the formula

YN-CN

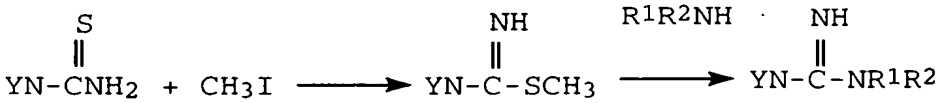
(VI)

with H_2S to obtain an N-thiocarboxamide YN-$CSNH_2$, which is reacted with an amine R^1R^2NH according to the two-stage equation



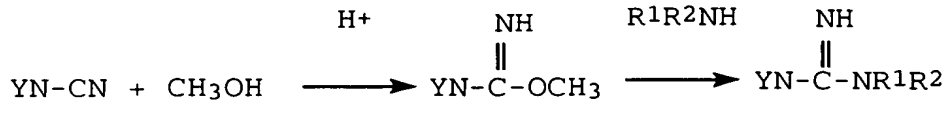
to yield compounds of the invention where Z is S and where Z is NH, or

(b) Methylating the N-thiocarboxamide to yield an isothiourea compound, which is in turn reacted with an amine R^1R^2NH:

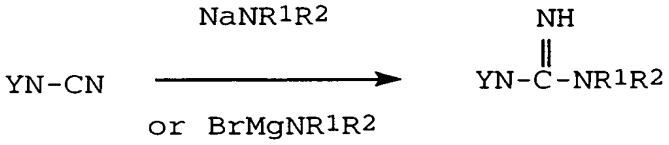


21. A method of synthesis of a compounds of formula (II) as defined in any one of Claims 8 to 13, comprising the step of reacting an N-cyano compound of

formula (VI) as defined in Claim 19 with methanol under acidic conditions to yield an isourea, which in turn is reacted with an amine according to the equation



22. A method of synthesis of a compound of formula (II) as defined in any one of Claims 8 to 13 in which Z is N, comprising the step of reacting an N-cyano compound of formula (VI) as defined in Claim 19, and a metallated residue



23. A composition comprising a compound according to any one of Claims 1 to 15, together with a pharmaceutically acceptable carrier.

24. A method of inducing analgesia, comprising the step of administering an effective amount of a compound according to any one of Claims 1 to 15 to a mammal in need of such treatment.

25. A method according to claim 24 in which the mammal is a human.

26. Use of a compound according to any one of Claims 1 to 15 in inducing analgesic.

27. Use of a compound according to any one of Claims 1 to 15 for the manufacture of a medicament for inducing analgesia.

Dated this 21st day of December, 1999
MONASH UNIVERSITY and POLYCHIP PHARMACEUTICALS PTY LTD
By their Patent Attorneys
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Fellows Institute of Patent and
Trade Mark Attorneys of Australia